

The Enforcement of Risk Evaluation and Mitigation Strategy (REMS)

By Anne K. Walsh

This article describes the evolution of Risk Evaluation and Mitigation Strategy (REMS) from a safety program to an enforcement tool. The potential pitfalls related to promotional activities are exacerbated by the statutory tools and public health implications associated with REMS. Companies should take heed of two cases that resulted in multi-million dollar payments and criminal charges for failing to follow FDA-imposed REMS requirements. Given the powerful resources available to the government, the key is to avoid scrutiny in the first instance. This article provides tips on how to minimize risk for drugs subject to REMS.

Overview

Even though a drug's professional labeling is the typical method for communicating safety information about a drug product, FDA can require a drug manufacturer to use Risk Evaluation and Mitigation Strategy (REMS) beyond the professional labeling to ensure the benefits of certain prescription drugs outweigh their risks. A REMS program squarely affects the advertising, promotion and labeling of a drug product.

FDA has authority to impose a REMS program as a condition for approval of a new drug, but FDA has exercised this authority sparingly since the statutory grant of this power in 2007. Indeed, in fiscal year 2018, FDA imposed a REMS requirement as a condition for approval of only two new drugs.^{1} FDA also can impose REMS requirements postapproval if it receives new safety information about an approved drug product from a clinical trial, an adverse event report, postapproval study, peer-reviewed literature or postmarket surveillance, among other things.

REMS are no longer a mere safety tool for FDA; rather FDA can and has used REMS as a powerful enforcement tool. Given the government's enforcement focus over the last two decades on off-label promotion (i.e., promotion for unapproved uses), a natural evolution for the government is to appraise a drug manufacturer's promotion as it relates to

safety information it conveys. In the last year, the government has used noncompliance with REMS as a basis for imposing significant civil and criminal penalties against drug companies. Therefore, companies should heed FDA's stated goals with respect to REMS programs, take note of the implications of a failure to comply with REMS requirements, ensure its employees follow the guidelines and be aware of potential pitfalls that could lead to exposure.

Requirements of REMS Programs

FDA considers the following six factors when determining whether a REMS program is warranted:

1. the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
2. the expected benefit of the drug with respect to the disease or condition
3. the seriousness of the disease or condition that is to be treated with the drug
4. whether the drug is a new molecular entity
5. the expected or actual duration of treatment with the drug
6. the estimated size of the population likely to use the drug

If FDA determines that a REMS program is necessary to mitigate the risks of the drug, the drug sponsor must develop a proposed REMS program for FDA review and approval. Each REMS program is unique, as it is intended to address specific safety measures tailored to the safety risks associated with a particular drug or class of drugs. The specific elements can include:

- A Medication Guide or Patient Package Insert.^{2} A Medication Guide is additional labeling required to be dispensed with the drug and written in non-technical language.
- A Communication Plan.^{3} The communication plan could include letters to healthcare providers or professional societies about the REMS or to explain the risks of the drug. These items may be deemed labeling.
- Elements to Assure Safe Use (ETASU).^{4} ETASU requirements are generally the most extensive elements of a REMS program because they require medical intervention by healthcare professionals who seek to prescribe or dispense the drug to the patient. These elements may require prescribers to have specific training/experience or special certifications; pharmacies, practitioners or healthcare settings that dispense the drug to be specially certified; the drug be dispensed only in certain healthcare settings (e.g., infusion settings, hospitals); the drug be dispensed with evidence of safe-use conditions such as laboratory test results; each patient using the drug be subject to monitoring and/or each patient using the drug be enrolled in a registry.
- An Implementation System.^{5} The company should take reasonable steps to monitor and evaluate the execution of the REMS by healthcare providers, pharmacists and others in the healthcare system who are responsible for those elements, and to work to improve their implementation.

REMS Enforcement

FDA uses a risk-based approach to select REMS programs for inspection each year. The risk-based approach takes into account factors such as:

- REMS with ETASU
- REMS with identified issues or violations from a previous REMS inspection
- REMS with approved modifications since the last inspection
- REMS that have been identified by the Office of New Drugs or Office of Surveillance and Epidemiology with recognized issues
- REMS with issues identified during review of the REMS assessment report
- REMS that have never been inspected
- REMS that have not been inspected in the last two to three years^{6}

A drug is misbranded under the *Federal Food, Drug, and Cosmetic Act (FDC Act)* if there is a violation of one of the following requirements of its REMS program:^{7}

REMS Observation	Citation
Failure to comply with REMS timetable for submission of assessments	FDC Act § 505-1(d)
Failure to comply with REMS medication guide	FDC Act § 505-1(e)(2)(a)
Failure to comply with REMS communication plan	FDC Act § 505-1(e)(3)
Failure to comply with REMS ETASU	FDC Act § 505-1(f)(3)(A)-(F)
Failure to comply with REMS implementation system	FDC Act § 505-1(f)(4)

It is a prohibited act under the *FDC Act* to introduce a misbranded drug into interstate commerce or to do an act that causes a drug to be misbranded while held for sale.^{8} Thus, a violation of a REMS requirement can result in FDA exercising one of its administrative options, like issuing an Untitled Letter or Warning Letter, or seeking civil monetary penalties. Factors that influence the issuance of an Untitled or Warning Letter include the nature and extent of the violations (e.g., repeat or deliberate misconduct), the compliance history of the inspected firm and the corrective actions implemented by the firm.^{9} FDA may impose civil monetary penalties of up to \$250,000 per violation of REMS requirements, not to exceed \$1 million in a single proceeding.^{10} Civil monetary penalties may increase if the violation continues more than 30 days after FDA notifies the applicant holder of the violation. The penalties double for the second 30-day period, and continue to double for subsequent 30-day periods, up to \$1 million per period and \$10 million per proceeding.

If FDA considers the conduct more egregious, FDA can refer the matter to the Department of Justice (DOJ) to pursue civil remedies, criminal prosecution or both. For example, FDA can initiate a seizure action against the drug subject to REMS or enjoin a drug company required to comply with REMS from continuing to market its product. And criminal charges may carry significant penalties against corporations or even potential jail time for individuals responsible for the violation.

REMS Enforcement Recent Expansion

Despite its statutory authority, FDA has not often brought enforcement action to punish companies who do not follow REMS requirements. Rather FDA has relied on its authority to modify REMS programs based on new safety information (which could include information that an existing REMS is not effective) or to issue Untitled or Warning Letters.^{11}

In the last year, however, FDA has brought two notable enforcement actions based on REMS violations, and DOJ has jumped on the bandwagon too. Using the already powerful tool of the *False Claims Act (FCA)*,^{12} DOJ's underlying theory is that a regulatory violation, such as a failure to follow a REMS requirement, means that the misbranded drug should not have been reimbursed by federal healthcare programs. Because the *FCA* offers the potential for significant recoveries, it is no surprise that the government has expanded the scope of potentially material activities to implicate *FCA* liability.

Novo Nordisk^{13}

In 2010, FDA approved Novo Nordisk's injectable drug Victoza (liraglutide injection) as an adjunct to diet and exercise to improve glycemic control in adults with Type II diabetes mellitus. Part of the data available to FDA during its review showed that some rodents exposed to Victoza developed thyroid C-cell tumors, but there were insufficient data to determine whether Victoza causes thyroid C-cell tumors in humans. Medullary Thyroid Carcinoma (MTC) is a rare form of thyroid tumor, and FDA required Victoza's approved labeling to contain a boxed warning about the unknown risk of MTC in humans.

FDA also required Novo Nordisk to develop a REMS with a Communication Plan to inform healthcare providers about the boxed warning of the unknown risk of MTC. Novo Nordisk agreed to send a letter to likely prescribers of Victoza, including primary care physicians and endocrinologists, and to disseminate a document titled "Highlighted Information for Prescribers" during sales calls to physicians.

According to the Complaint, however, Novo Nordisk did not appropriately train its sales representatives on how to implement the Communication Plan, and in fact provided them with information to counter and neutralize the MTC risk message. Specifically, the government focused on a skit performed during the launch meeting that implied that the risk of MTC existed only in rodents; and coaching by managers to “sandwich” information about the MTC risk in between promotional messages about the efficacy of Victoza. The government had evidence that the sales representatives implemented this messaging, in addition to other types of statements that:

- All diabetes drugs have boxed warnings, so Victoza is no different than other diabetes drugs.
- It is implausible that humans could contract MTC given the differences between rats and humans.
- MTC is easy to treat, so of little concern.

This evidence likely came from, or was developed by, the seven different whistleblower complaints filed against Novo Nordisk for violations of the *False Claims Act*.

Further, as part of the REMS-required Implementation System, Novo Nordisk conducted surveys of endocrinologists and primary care physicians to gauge their awareness and understanding of the unknown risk of MTC associated with Victoza. The survey showed that a significant number of primary care physicians, compared to endocrinologists, were not aware of the boxed warning on the Victoza labeling. FDA told the company that the “lack of knowledge among primary care physicians of the boxed warning for thyroid C-cell tumors” was new safety information and required the company to modify the REMS by preparing and disseminating a letter specific to primary care physicians (which FDA reviewed and approved).

Again, according to the Complaint, Novo Nordisk did not appropriately train its representatives around dissemination of the letter. The company instructed its sales force in a recorded voice mail message from the vice president of marketing that there are “no new safety or additional safety concerns” and that the letter was “part two” of the same REMS requirement, which FDA deemed to contravene the REMS modification focused on ensuring that primary care physicians were made aware of the potential risks of Victoza.

Because the company failed to comply with the requirements of the REMS Communication Plan, FDA deemed Victoza to be misbranded and the shipment of misbranded Victoza a prohibited act in violation of the *FDC Act*. FDA sought and the company agreed to disgorge \$12.15 million, to account for sales of Victoza between February 2010 and December 2012. The government also sought and received a \$46.5 million payout under the *False Claims Act* for the same conduct, coupled with additional allegations of off-label promotion of Victoza for patients who did not have Type II diabetes, a condition FDA had not approved. The settlement resolved seven separate lawsuits filed by private parties against Novo Nordisk in the District of Columbia. The global \$58 million settlement was announced in September 2017.

Aegerion{14}

In contrast to Novo Nordisk, the conduct of Aegerion was more wide-ranging and egregious and resulted in civil and criminal penalties for a violation of several statutes, not just the *FDC Act*. It is unknown whether the government’s investigation would have been as far-reaching had the company complied with its REMS requirements in the first instance.

Familial Hypercholesterolemia (FH) is a genetic disorder that prevents the removal of the “bad” cholesterol from the blood. If a person inherits the defective receptor gene from one parent, that person has heterozygous FH (HeFH); if a person inherits the receptor gene from both parents, that person has homozygous familial hypercholesterolemia (HoFH). A person with HoFH develops early and severe atherosclerotic cardiovascular disease, which could lead to heart attack, stroke and death.

Aegerion sought approval for Juxtapid as an orphan drug, which gave the company access to certain benefits for drug products intended to treat diseases and conditions affecting fewer than 200,000 people. Before approval, Aegerion had engaged in several discussions with FDA about the scope of approval, namely whether Juxtapid also could be considered for refractory (i.e., resistant to treatment) HeFH. FDA told Aegerion that such

an expanded indication would require an additional clinical trial. In December 2012, FDA approved Juxtapid as an adjunct to other lipid-lowering therapies to treat adult patients with HoFH. The FDA-approved labeling included a boxed warning cautioning prescribers about the risk of liver toxicity when taking Juxtapid, and FDA required Aegerion to develop a REMS program to ensure the benefits of the drug outweighed the risk of liver toxicity. Specifically, FDA required Aegerion to educate prescribers about the risks of hepatotoxicity (liver toxicity) associated with the use of Juxtapid and the need to monitor patients who are treated with Juxtapid and ensure that Juxtapid is prescribed and dispensed only to those patients with a clinical or laboratory diagnosis consistent with HoFH. The elements to assure safe use included training for physicians and an attestation from prescribers that each new prescription was for a patient who had a diagnosis consistent with HoFH.

According to the government's Complaint, the company violated several components of the REMS program:

- Elements to assure safe use: Aegerion sales representatives allegedly provided healthcare providers with incomplete, inaccurate and misleading information about HoFH. Specifically, Aegerion falsely obtained physician attestations by misrepresenting the scope of HoFH, used prescribers' signature stamps without their knowledge and misused nurse practitioners in place of the physicians who were required to sign off on the attestation.
- Implementation plan: Aegerion allegedly defined HoFH vaguely to capture additional patient populations beyond the orphan population originally discussed with FDA. FDA considered this a violation of the implementation plan. Aegerion also allegedly filed a misleading REMS assessment report that failed to disclose the company's strategy for promoting Juxtapid inconsistent from its preapproval filings with FDA.
- On 8 November 2013, FDA issued a Warning Letter to Aegerion for minimizing the boxed warning about liver toxicity. FDA requested the company submit "a comprehensive plan of action to disseminate truthful, non-misleading and complete corrective messages about the issues discussed in this letter to correct any misimpressions about the approved use of Juxtapid." The company's corrective action was insufficient and on 22 September 2017, the company entered into a global resolution with the government. The settlement included:
 - The company agreed to plead guilty to two misdemeanor violations of the *FDC Act* for the REMS violations and off-label promotion of Juxtapid, resulting in \$7.2 million in criminal fines and forfeiture.
 - The company also agreed to pay \$28.8 million to resolve claims that the company's promotional activities, including the allegedly false and misleading statements in contravention of the REMS program, violated the *False Claims Act*.
 - The company entered into a Deferred Prosecution Agreement to resolve charges of conspiracy to violate the *Health Insurance Portability and Accountability Act (HIPAA)*. Specifically, the government alleged the company sought to use *HIPAA*-protected health information to identify patients not previously diagnosed as having HoFH.
 - A settlement with the Securities and Exchange Commission relating to the company's disclosure practices.
 - In total, the company agreed to pay more than \$35 million to resolve civil and criminal claims against it.

Strategies for Avoiding Enforcement

Although a REMS program may be unavoidable with the approval of certain drug products, a multi-million dollar resolution for violations of the REMS program is completely avoidable. Companies can benefit from lessons learned from the above-described cases.

First, there is no doubt there would have been no government action if companies did not attempt to undermine the purpose of the REMS. Because the discussion of safety issues may undermine increased sales of a drug, the sales force should be trained about the history and basis for FDA's concerns and the scope of approval. Perhaps the Juxtapid representatives would not have been as aggressive had they understood the company had agreed to limit the patient population during the preapproval discussions about the

drug. Companies should prioritize adequate training for those that will be responsible for compliance with REMS implementation, and also think critically as to whether any policies, procedures or compensation plans incentivize improper conduct.

Second, companies should establish a plan for addressing noncompliance with the REMS program requirements both with company employees and external REMS participants. REMS participants are stakeholders who participate in the REMS based on their role in clinical assessment, prescribing, dispensing, administering or monitoring, as well as the distribution process. These stakeholders can include healthcare providers who prescribe, patients who receive the drug, healthcare settings, practitioners, pharmacies that dispense and wholesalers/distributors that distribute.

Third, companies should establish a track record of taking swift corrective action if noncompliance is identified. This may include voluntary disclosure to FDA of the violation. Although a difficult pill to swallow, a Warning Letter is much less painful than a drawn out investigation that could encompass several other issues beyond the REMS program.

Last, REMS requirements should be considered in the review of promotional materials to ensure safety information is clearly disclosed and any additional requirements are communicated to the physician and/or patient. Companies should continuously monitor compliance internally and with REMS participants to ensure the requirements of the REMS are being met. Companies should maintain adequate records to demonstrate that the REMS requirements are being met. This includes distribution and dispensing information, certification of pharmacies or healthcare settings, as applicable and audits of REMS participants.

Conclusion

The Novo Nordisk and Aegerion cases are cautionary tales of the consequences of neglecting postmarket requirements. With the government's increasingly creative interpretation of liability under the *FCA*, sponsors must not only be vigilant to comply with activities historically subject to *FCA* enforcement, such as off-label promotion, but with countless other regulatory requirements like the REMS program. It is critical that companies subject to REMS establish at the outset the right procedures to ensure compliance beyond normal promotional guidelines. Proper training of relevant employees is necessary to support a robust compliance program, as employees are better able to identify potential problems if they are informed of the proper regulatory requirements and the consequences for failing to comply.

References

1. Number of REMS approved. FDA website. <https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=cder&id=CDER-RRDS-Number-of-REMs-reviews-assessments-modifications>. Accessed 10 January 2019.
2. FDC Act § 505-1(e)(2); 21 C.F.R. § 208.
3. FDC Act § 505-1(e)(3). Note that it is not necessary for ANDA (generic) products to include a Communication Plan with its REMS program.
4. FDC Act § 505-1(f)(3).
5. FDC Act § 505-1(f)(4).
6. Compliance Program 7353.001c – Postmarketing Surveillance and Epidemiology: Human Drug and Therapeutic Biological Products. FDA website. <https://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM602307.pdf>. Accessed 10 January 2019.
7. FDC Act § 502(y).
8. FDC Act § 301(a), (k).
9. *Ibid*.
10. FDC Act § 303(f)(4)(A).
11. See, e.g., Untitled Letter from FDA to Adolor (21 April 2010) (claiming sales representative made a statement during a conference minimizing the importance of the REMS program by stating the program is “due to logistics”); Untitled Letter from FDA to Gilead Sciences, Inc. (27 February 2009) (claiming sales representative made a statement that the REMS for Letairis is “only there because of the class” and that it is “not that big of a deal”); Warning Letter from FDA to King Pharmaceuticals, Inc. (8 October 2009) (claiming promotional materials minimized the serious risks associated with Embeda by omitting serious and potentially fatal risks associated with the drug).
12. 31 U.S.C. § 3729(a)(1)(A), (B).
13. Novo Nordisk Agrees to pay \$58 Million for Failure to Comply with FDA-Mandated Risk Program. Department of Justice website. <https://www.justice.gov/opa/pr/novo-nordisk-agrees-pay-58-million-failure-comply-fda-mandated-risk-program>. 5 September 2017.
14. Drug Maker Aegerion Agrees to Plead Guilty; Will pay More Than \$35 Million to Resolve Criminal Charges and Civil False Claims Allegations. Department of Justice website. <https://www.justice.gov/opa/pr/drug-maker-aegerion-agrees-plead-guilty-will-pay-more-35-million-resolve-criminal-charges-and>. 22 September 2017.

About the Author

Anne K. Walsh is a director at Hyman, Phelps & McNamara, PC. She counsels clients on compliance and enforcement issues, including FDA inspections, seizure and injunction actions, warning letters and recalls. She focuses on defending companies against allegations of fraud related to marketing and promotion, cGMP and QSR, healthcare and clinical studies, with particular

emphasis on cases involving joint criminal and civil investigations under the *FDCA* and the *False Claims Act (FCA)*. She also has successfully sued the government for violating the *Administrative Procedure Act (APA)*. She applies her enforcement expertise to aid companies in compliance efforts, via internal investigations or risk assessment audits. She graduated from William and Mary with a JD. She can be contacted at AWalsh@hpm.com.

Cite as: Walsh AK. "The Enforcement of Risk Evaluation and Mitigation Strategy (REMS)." *Regulatory Focus*. January 2019. Regulatory Affairs Professionals Society.

© 2019 by the Regulatory Affairs Professionals Society. All rights reserved.